A Multiple-Dose Phase I Study of Intranasal Hydromorphone Hydrochloride in Healthy Volunteers

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We evaluated the pharmacokinetics, tolerability, and safety of 1 and 2 mg of intranasal hydromorphone hydrochloride in an open-label, single- and multiple-dose study. This Phase I study was conducted in 24 healthy volunteers (13 men and 11 women). Intranasal doses were delivered as 0.1-mL metered-dose sprays into one or both nostrils for 1- and 2-mg doses, respectively. Venous blood samples were taken serially from 0 to 12 h after the first single dose and the last (seventh) multiple dose. Plasma hydromorphone concentrations were determined by liquid chromatography/mass spectrometry/mass spectrometry. Noncompartmental analysis was used to estimate pharmacokinetic variables. After 7 intranasal doses of 1 and 2 mg (once every 6 h), mean ± SD peak plasma concentrations of 2.8 ± 0.7 ng/mL and 5.3 ± 2.3 ng/mL, respectively, were observed. The median time to peak concentration was 20 min for both single and multiple doses. Dose proportionality was observed for the 1- and 2-mg doses. Adverse events included somnolence, dizziness, and bad taste after dose administration. Intranasal hydromorphone hydrochloride was well tolerated and demonstrated rapid nasal drug absorption and predictable accumulation. These results support clinical investigation of hydromorphone hydrochloride nasal spray for use as an alternative to oral and IM administration.

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Pain management specialists have explored alternative routes to optimize the pharmacological management of pain (1–5). Investigators have noted that most cancer pain patients benefit from, and often require, an alternative route for opioid administration in the terminal stages of their disease; routes of administration are often rotated for convenience and for better control of pain intensity and adverse effects. Some patients are unable to take drugs orally for some periods because of the gastrointestinal side effects of opioids or inability to swallow, and acute exacerbation of pain may require a change in the route of opioid administration (1,2). In acute pain settings, such as early management of postoperative pain, an alternative to administration by injection can also be desirable, particularly if absorption is more rapid than with oral administration.

Although the intranasal route has been shown to be effective for delivery of a variety of opioid analgesics, only butorphanol tartrate is commercially available for use by this route. Despite the great interest in nasal delivery of opioids, evaluation of multiple-dose pharmacokinetics of systemically-acting intranasal drugs is very limited. In a previous study, we examined the pharmacokinetics and bioavailability of hydromorphone after single intranasal doses compared with IV administration (6). Hydromorphone's medium duration of clinical activity and short elimination half-life require that it be given every 3–4 h. Hence, repeated short-term administration is likely to occur in the treatment of acute pain. For this reason, the objectives of this study were to examine the pharmacokinetics and tolerability of this investigational hydromorphone hydrochloride (HCl) nasal spray after repeated administration for 42 h.

Methods

Twenty-four healthy nonsmoking subjects (13 men and 11 women) between the ages of 18 and 36 yr (23.5 ± 6.1 yr, mean ± SD) and weighing 59 to 100 kg (men, 78.0 ± 11.3 kg; women, 65.2 ± 6.3 kg) participated in

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this inpatient study after written, informed consent (as approved by the Medical IRB of the University of Kentucky) was obtained. Three volunteers were African American, one was Hispanic, and 20 were Caucasian. All were within ±20% of ideal body weight in relation to height and body frame (per Metropolitan Life Insurance tables). Subjects had no history of allergies, nasal symptoms, clinically significant previous nasal surgery, trauma, polyps, or other physical abnormalities of the nose. Subjects abstained from all medications from the date of screening until the end of the study. They also abstained from alcohol and caffeine 48 h before the dosing period and during the study. This study was conducted according to the applicable guidelines for good clinical practice.

The intranasal hydromorphone HCl formulation, an aqueous solution buffered to pH 4.0 with 0.2% sodium citrate and 0.2% citric acid, provided 1 mg of hydromorphone HCl in a 0.1-mL spray from a commercially available unit dose-metered spray pump. The composition of the solution was identical to the Dilaudid-HP® product (hydromorphone HCl 10 mg/mL; Knoll Pharmaceutical Co., Mount Olive, NJ, a division of Abbott Laboratories) and was prepared under good manufacturing practices conditions in the University of Kentucky College of Pharmacy Center for Pharmaceutical Science and Technology.

Subjects were randomly assigned to receive either 1 or 2 mg of hydromorphone HCl in this open-label, single- and multiple-dose study. All subjects received the single dose first (Dose S1) and returned approximately a week later for the multiple-dose treatment (Doses M1–M7), during which they received the same dose (1 or 2 mg) as in the single-dose treatment. Multiple-dose treatments of intranasal hydromorphone HCl were given every 6 h beginning at approximately 8:00 PM so that the M7 dose was given around 8:00 AM. Subjects fasted for 8 h before and 1 h after dosing for the single dose (except for water *ad libitum* and a caffeine-free drink at least 1 h before dosing). During the multiple-dose treatment, the subjects fasted for 1 h before and after intranasal dose administration. Subjects were provided standardized xanthine-free meals and snacks at preset times each day they were institutionalized.

Immediately before study drug administration, the subject gently blew his or her nose. Hydromorphone HCl nasal spray was administered by a physician or research nurse, who directed the spray toward the lateral nasal wall. Each subject received a single spray into one nostril for the 1-mg dose or a single spray into each nostril for a total of 2 mg. After study drug administration, the subject remained in a semirecumbent position for 10 min and refrained from blowing his or her nose for at least 60 min. During the multiple-dose treatment, subjects remained in the hospital room and refrained from vigorous activity throughout the study period.

For Doses S1 and M7, serial venous blood samples were obtained according to the following schedule: 0 (predose), 5, 10, 15, 20, 30, and 45 min and 1, 2, 3, 4, 6, 8, and 12 h after drug administration. During the multiple-dose treatment, trough samples were drawn within 10 min before Doses M1 and M4 through M7. Venous blood samples were collected by using 10-mL heparinized Vacutainer® tubes. Plasma was separated from blood cells by centrifuging at 4°C, transferred to polypropylene tubes, and stored at approximately −70°C. Frozen plasma samples were then shipped to AAI Development Services, Inc. (Shawnee, KS) for hydromorphone assay.

Plasma hydromorphone concentrations were determined with a liquid chromatography/mass spectrometry/mass spectrometry assay developed by AAI Development Services. The assay was validated for specificity, sensitivity, linearity, stability, dilution, precision, accuracy (recovery), and reproducibility. Hydromorphone and the added internal standard, hydromorphone-d_3, were extracted from human plasma by using a solid-phase extraction. Reconstituted extracts were analyzed by using a TurboIonSpray Ion Source inlet and a multiple reaction monitoring protocol. The method is linear over the range of 0.02–2.0 ng/mL. Concentrations <0.02 ng/mL were reported as below the quantitation limit. Samples with concentrations larger than 2.0 ng/mL were reanalyzed by using a dilution so that the assayed concentrations were within the range of 0.02–2.0 ng/mL. Between-day and within-day accuracy and precision were <12% of the relative standard deviation (SD).

A physician was present in the clinic for each dose administration and for at least 4 h after Doses S1 and M7 of study drug. Arterial blood pressure, heart rate, and respiratory rate were measured before and at 0.5, 1, 3, and 6 h after Doses S1 and M7 and 1 h after Doses M1 through M6. In addition to recording spontaneously reported subjective symptoms, a research nurse also questioned subjects about adverse events each time vital signs were recorded. The severity of each adverse event was classified as mild, moderate, or severe by using standard definitions (6). Nasal examinations by an otolaryngologist to evaluate local mucosal irritation or damage were performed at screening; before Doses S1 and M7; at 2–4 h after Doses S1, M3, and M7; and at the end of the study.

Pharmacokinetic variables were characterized by using standard noncompartmental methods (7) with log-linear least-square regression analysis (weighting factor $1/y$) to determine the elimination rate constants by using WinNonlin (Version 3.2; Pharsight Corp., Palo Alto, CA). Maximum plasma concentration and time to maximum plasma concentration (C_{max} and t_{max}, respectively), elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve from Time 0

to infinity ($AUC_{0-\infty}$), from Time 0 to the last measurable time point (AUC_{0-t}), and, for the multiple-dose profiles, partial areas for the 6-h dosing interval (AUC_{0-6}) were calculated. All AUCs were determined by WinNonlin by using a combination of the linear and logarithmic trapezoidal rules. The average concentration for multiple-dose data was computed as AUC_{0-6} divided by 6 h. Mean concentrations for the graphs were calculated by using only concentration-time points that were drawn within 5% of the time planned by the protocol (657 of 672 planned time points were used). Simulated mean concentrations after repeated dosing to steady state were generated by using the principle of superposition and the mean plasma concentrations and terminal elimination constant from the 2-mg single-dose data (7).

Data are reported as mean and SD or median and range when appropriate. Statistical analyses were performed with PC-SAS (Version 6.12; SAS Institute, Cary, NC). The statistical tests were two sided, with a critical level of 0.05. The analysis of variance (ANOVA) models included the factors subject and dose for single- versus multiple-dose comparison and the factors subject and dose number for trough level comparison. ANOVA of the dose-normalized variables AUC and C_{max} was performed to assess the dose proportionality of the variables after single- and multiple-dose treatments. *P* values are from the ANOVA with the factor dose group. The sex effect for all treatments was analyzed by using an ANOVA of log-transformed AUC and C_{max} with the factors sex, treatment (1 versus 2 mg), and dose.

Results

All 24 subjects completed the study. Absorption of hydromorphone after intranasal administration was rapid (detected within 5 min in all subjects), and its disappearance from plasma was multiphasic. Mean plasma hydromorphone concentration-versus-time profiles ($n = 12$ per profile) are shown in Figure 1. Mean pharmacokinetic variables from the noncompartmental analysis of measured plasma concentrations are presented in Table 1. Wide intersubject variability in pharmacokinetic variables was reflected in the SD for most variables. Furthermore, predose hydromorphone concentrations ranged from 0.41 to 0.89 ng/mL and peak concentrations from 1.8 to 4.3 ng/mL for the 1-mg dose (M7). Predose concentrations ranged from 0.82 to 1.5 ng/mL and peak concentrations ranged from 2.2 to 10.5 ng/mL for the 2-mg dose (M7). No significant difference was found between t_{max} values for the single and multiple doses, with median t_{max} values of 20 min for all 4 doses (overall range, 10–60 min). Comparison of dose-normalized pharmacokinetic variables after single and multiple dosing demonstrated no significant differences in C_{max}, AUC_{0-t}, or $AUC_{0-\infty}$ ($P > 0.3$). These findings indicate dose-proportional pharmacokinetics for 1- and 2-mg intranasal doses. The $t_{1/2}$ values were independent of dose level after single doses ($P > 0.8$), but not after multiple doses ($P < 0.05$), for which the $t_{1/2}$ estimate was longer for the 2-mg multiple dose.

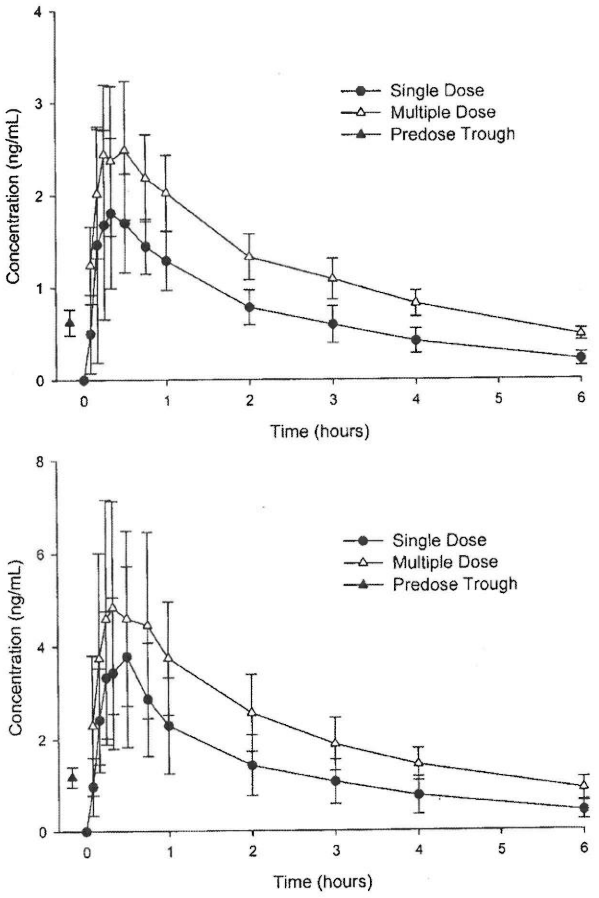

Figure 1. Hydromorphone plasma concentrations (mean ± SD bars) after intranasal 1-mg (top) and 2-mg (bottom) doses of hydromorphone HCl ($n = 12$ subjects for each dose). Profiles are after a single dose (S1) and after repeated doses every 6 h for 42 h (multiple doses; M7). Mean predose M7 trough concentrations are shown as filled triangles.

Overall, women had larger plasma concentrations than men. Sex effects were statistically significant for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} after the 2-mg single dose ($P = 0.0016$, 0.0006, and 0.0183, respectively) and for AUC_{0-6} after the 1- and 2-mg multiple doses ($P = 0.0107$ and 0.0008, respectively). After the 2-mg single dose, mean $AUC_{0-\infty}$ values were 7.9 ± 1.9 ng · h/mL and 14.2 ± 3.1 for men ($n = 7$) and women ($n = 5$), respectively. Mean C_{max} values were 3.2 ± 0.53 ng/mL and 5.4 ± 2.0 ng/mL for men and women, respectively. After the 2-mg multiple doses, mean AUC_{0-6} values were 10.7 ± 2.0 ng · h/mL and 16.9 ± 2.3 ng · h/mL for men and women, respectively.

Table 1. Mean[a] (SD) Single-Dose (Dose S1) and Multiple-Dose (Dose M7) Hydromorphone Pharmacokinetic Variables After Administration of 1 and 2 mg of Intranasal Hydromorphone HCl in Healthy Volunteers (n = 12 for Each Dose)

Treatment	t_{max} (h)[a]	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng · h/mL)	$t_{1/2}$ (h)	AUC_{0-6} (ng · hr/mL)	C_{avg} (ng/mL)
S1 (1 mg)	0.33 (0.17–1.0)	2.4 (0.9)	5.6 (1.1)	4.4 (1.5)	—	—
M7 (1 mg)	0.33 (0.17–1.0)	2.8 (0.7)	10.8 (1.3)	4.4 (1.1)	7.1 (1.1)	1.2 (0.2)
S1 (2 mg)	0.33 (0.17–0.75)	4.1 (1.7)	10.5 (4.0)	4.3 (1.7)	—	—
M7 (2 mg)	0.33 (0.17–1.0)	5.3 (2.3)	22.3 (8.3)	6.4 (2.9)	13.3 (3.8)	2.2 (0.6)

S1 = single dose; M7 = multiple dose (1 or 2 mg every 6 h for seven doses); t_{max} = time to maximum plasma concentration; C_{max} = maximum plasma concentration; $t_{1/2}$ = elimination half-life; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from Time 0 to infinity; AUC_{0-6} = area under the plasma concentration-time curve from Time 0 to 6 h; C_{avg} = average concentration after multiple dosing.

[a] Data are mean (SD), except median and range are given for t_{max}.

The ratios and 95% confidence intervals for (AUC_{0-6} after multiple dose)/($AUC_{0-\infty}$ after single dose) were 1.28 (1.10–1.49) and 1.30 (1.15–1.47) for the 1- and 2-mg doses, respectively. An AUC ratio of unity would indicate time-invariant kinetics for single and multiple dosing. The 95% confidence interval for the AUC ratio did not include unity, however, suggesting that time-invariant kinetics (linear kinetics) were not definitively demonstrated.

Attainment of steady-state was assessed by testing predose (trough) concentrations for Doses M5, M6, M7 and a theoretical M8 dose for statistically significant differences. The additional trough concentration was calculated as follows: assuming the 6-h dosing regimen had continued, the concentration at 6 h after Dose M7 was considered the trough concentration before a hypothetical eighth dose, M8. Statistical analysis of trough concentrations taken before Doses M5, M6, and M7 (Table 2) indicated that hydromorphone plasma concentrations were apparently still increasing during the night hours after 42 h of dosing every 6 h. Concentrations declined, however, at 6 h after Dose M7 (comparison of troughs for Dose M7 and hypothetical Dose M8, $P < 0.0002$), suggesting that concentrations had reached steady-state.

A simulation of steady-state plasma hydromorphone concentrations was performed to demonstrate how well the single-dose kinetics of hydromorphone predicted multiple-dose plasma concentrations. Mean plasma concentrations of hydromorphone after the 2-mg single dose of hydromorphone HCl (n = 12 subjects) were used to predict multiple-dose concentrations by using the superposition method (7). Figure 2 shows simulation curves (dotted line) with measured plasma concentrations from the multiple-dose studies. The actual mean trough and mean multiple-dose concentrations are shown. The excellent agreement between the simulated and actual concentrations demonstrates predictable kinetics.

All 24 subjects completed the study without serious adverse events. The most common drug-related adverse events are summarized in Table 3. A drug-related adverse event was defined as an event with a relationship to the study drug judged to be possible, probable, or highly probable. A subject was counted at most once for multiple occurrences of an adverse event. Adverse events were similar to those reported in earlier studies (6,8), and all were resolved before subjects were discharged.

Adverse events were dose related and generally mild to moderate in severity. Most subjects reported a bad taste immediately after the intranasal doses, but this sensation resolved in less than 1 h in all cases. Although some (25% for multiple dose only) reported brief nasal itching, no mucosal irritation was seen on early or follow-up nasal evaluations. Itching was also noted in the face, head, and pubic area. Several subjects reported nasal stuffiness/congestion, and two reported brief nasal stinging. The most common adverse events seen with nasal administration were ones frequently associated with hydromorphone, e.g., somnolence, dizziness, nausea and euphoria, and asthenia (feelings of tiredness, weakness, or heaviness in the limbs or body). Overall, 83% and 92% of the subjects had at least one drug-related adverse event after the 1- and 2-mg single-dose treatments, respectively. Approximately 92% and 100% of the subjects had at least one drug-related adverse event after the 1- and 2-mg multiple-dose treatments, respectively. There were no clinically relevant changes in vital signs. Arterial blood pressure and heart rate remained within the normal ranges throughout the study for all subjects. Importantly, no respiratory depression (decreased rate, decrease in oxygen saturation, or reports of respiratory symptoms) occurred after intranasal hydromorphone HCl administration in any subject.

Discussion

Our prior investigations have focused on single-dose pharmacokinetics of intranasal hydromorphone HCl (6,9,10). This study was conducted at the same institution as our previous study (6) and is the first to report the pharmacokinetics of hydromorphone after repeated intranasal administration of 1- and 2-mg doses every six hours for seven doses. We found that absorption was consistently rapid (median peak times

Table 2. Summary of Analysis of Predose (Trough) Concentrations After 1 and 2 mg of Intranasal Hydromorphone HCl Every 6 Hours for 42 Hours

Variable	Trough hydromorphone concentration			
	1-mg dose (ng/mL)	*P* value (doses compared)	2-mg dose (ng/mL)	*P* value (doses compared)
Predose M5	0.479 (0.12)		0.881 (0.26)	
Predose M6	0.496 (0.11)	0.0006 (M5, 6, 7, 8)	1.055 (0.32)	0.0002 (M5, 6, 7, 8)
Predose M7	0.622 (0.14)	0.0004 (M6, 7, 8)	1.186 (0.22)	0.0013 (M6, 7, 8)
Predose "M8"	0.479 (0.065)	0.0031 (M7, 8)	0.902 (0.25)	0.0002 (M7, 8)

P values are from an analysis of variance with factors subject and dose number. Means (SD) are given (n = 12 for each concentration).

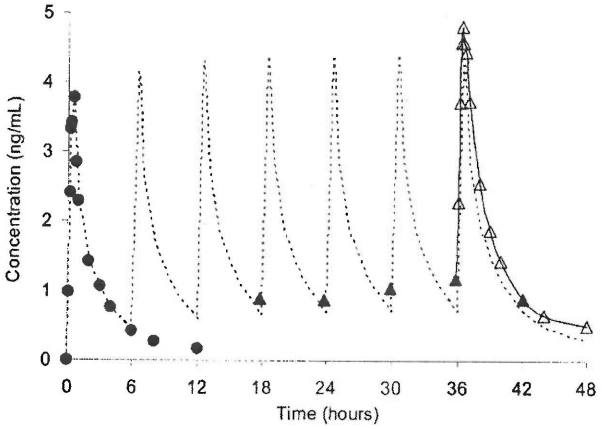

Figure 2. Steady-state multiple-dose plasma hydromorphone concentrations were predicted from the single-dose data by using the superposition method. Mean plasma concentrations of hydromorphone after the single dose of 2 mg of intranasal hydromorphone HCl (Dose S1; ●) were used to predict multiple-dose concentrations for seven doses. The dotted line represents the S1 plasma concentrations (0–12 h) followed by simulated concentrations (6–48 h). Mean troughs (Doses M4–M7) and Dose M7 actual concentrations are also shown as filled and open triangles, respectively, superimposed on the simulated profile. Note that, although shown this way, the S1 dose was not the first dose of the multiple-dosing part of the study, but was given approximately a week before the multiple-dose part of the study.

of 20 minutes) and that there were no unexpected side effects from repeated nasal administration. Hydromorphone accumulated approximately 20%–30% after repeated administration every 6 hours for 42 hours compared with single-dose administration.

Although hydromorphone has been used for the treatment of moderate to severe pain for 75 years, there is a paucity of pharmacokinetic data in the literature (6,8–18). The few studies of hydromorphone were recently reviewed by Sarhill et al. (8). Previous reports establish that orally administered hydromorphone undergoes extensive first-pass metabolism, resulting in a bioavailability of approximately 51% (12). Previous studies also reported the average times to peak plasma concentration as 1 and 1.5 hours after oral tablet and rectal administration, respectively (11,12). Mean times to C_{max} were 0.75 ± 0.31 hours and 1.01 ± 0.82 hours, and C_{max} values were 5.12 ± 3.1 ng/mL and 4.09 ± 2.1 ng/mL in women and men, respectively, for immediate-release 8-mg Dilaudid-IR tablets (Knoll) (17). More than 80% of the t_{max} values in this study were ≤30 minutes. Considering that after the single 2-mg intranasal dose in this study, mean C_{max} values were 3.2 and 5.4 ng/mL for men and women, respectively, dose normalization shows that the intranasal formulation achieved approximately 3- or 4-fold larger peak concentrations per milligram compared with the oral 8-mg tablets. The results of this study in 24 healthy volunteers show that the intranasal formulation of hydromorphone HCl achieved greater plasma levels compared with oral tablets and a more rapid absorption compared with oral tablets and rectal suppositories. Thus, the intranasal route is likely to be particularly useful in clinical settings where rapid absorption is needed but where injection is undesirable.

The mean half-lives (approximately 6 hours) were longer in this study compared with our previous study in healthy volunteers (average 4.6 hours) (6), and earlier ones that were reported in the literature (2–3 hours) (12,16). Comparison of previous investigations suggests that blood sampling time (range, 6–24 hours), assay sensitivity, and other factors have contributed to the differences in estimates. Using a longer blood sampling period (24 hours) and a sensitive assay (limit of detection, 0.05 ng/mL), one investigation in young adult volunteers revealed a slow terminal elimination phase with a half-life of approximately 12 hours that started approximately 8 hours after dosing, and it was suggested that the elimination rate constant was poorly defined because of secondary peaking due to biliary cycling (18). We also saw secondary peaking around three to six hours in many individuals, and this is probably reflected in our half-life estimation.

We observed statistically significant differences in AUC values and peak plasma concentrations between men and women, with women averaging higher values than men. We observed similar trends in our previous study but did not report them (6). A closer examination of the previous data revealed similar, statistically significant sex differences, in the same direction, for AUC_{0-t} and $AUC_{0-\infty}$ but not for C_{max}.

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